REMARKS

Applicants acknowledge the renumbering of the claims. The Examiner rejected claims 9, 15, and 34-43 and 45-67, while objecting to claim 44. Claims 34, 36, 44, 45, 52, 54, 62, and 63 have been cancelled herein without prejudice. In addition, claims 9, 15, 40, and 59 have been amended. In particular, claims 9 and 15 have been amended to incorporate the language from dependent claims 44 and 62, respectively. Claims 40 and 59 have been amended to replace the word "is" with the word "encodes" as suggested by the Examiner. No new matter has been added.

In light of the following remarks, Applicants respectfully request reconsideration and allowance of claims 9, 15, 35, 37-43, 46-51, 53, 55-61, and 64-67.

Claim Objections

The Examiner objected to claims 45 and 63 because of a misspelling. Claims 45 and 63 have been cancelled without prejudice. Thus, these objections are moot.

The Examiner also objected to claim 44 as being dependent upon a rejected base claim, stating that claim 44 would be allowable if rewritten in independent form. Claim 44 has been cancelled herein without prejudice. In addition, claim 9 has been amended to incorporate the language recited in claim 44. Thus, this objection is moot.

Objections to the Specification

The Examiner objected to the disclosure since it contains embedded hyperlinks and/or other forms of browser-executable codes at page 13, line 1 and page 15, line 4. The specification has been amended at page 13, line 1 and page 15, line 4 to remove the embedded hyperlinks. No new matter has been added.

In light of the above, Applicants respectfully request withdrawal of the objections to the specification.

Rejections under 35 U.S.C. § 112, second paragraph

The Examiner rejected claims 40 and 59 under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which

applicant regards as the invention. Specifically, the Examiner stated that it is unclear how GALVenv, HSVTK, cytosine deaminase, nitroreductase, and VSV-G glycoprotein can be a gene, suggesting the substitution of the term "is" for the term "encodes."

Claims 40 and 59 have been amended as suggested. In light of these amendments, Applicants respectfully request withdrawal of the rejection of claims 40 and 59 under 35 U.S.C. § 112, second paragraph.

Rejections under 35 U.S.C. § 112, first paragraph

The Examiner rejected claims 9, 15, 34-43, and 45-67 under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. Specifically, the Examiner stated that:

> apart from the exemplification showing the highly tissue-specific heat shock element (HSE)-Tyr-300/heat shock factor-1 (HSF-1) feedback loop system that can be used to kill melanoma cells specifically and efficiently, the instant specification fails to teach a representative number of species of a nucleic acid comprising any cell-type specific promoter in combination with any amplification promoter element and any sequence encoding a transcription factor that activates the amplification promoter element, and said nucleic acid produces a level of mRNA expression which is at least 100-fold higher in *in vitro* cells of the specific cell type compared to *in vitro* cells which are not of the specific cell type.

The Examiner also stated that:

> The skilled artisan cannot fully envision the detailed structure of a nucleic acid comprising any cell type-specific promoter in combination with any amplification promoter element and any sequence encoding a transcription activator that activates the amplification promoter as claimed apart from the disclosed HSE-Tyr-300/HSF-1 feedback loop nucleic acid system, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method.

Applicants respectfully disagree. A person having ordinary skill in the art at the time Applicants filed would have appreciated that Applicants' specification adequately describes the subject matter of the originally claimed invention. To further prosecution, however, independent

claims 9 and 15 have been amended to recite that the amplification promoter element is an HSE and the transcription activator is HSF-1.

Applicants' specification adequately describes the subject matter of these amended claims. In fact, Applicants' specification discloses multiple examples of cell type-specific and tissue-specific promoters. For example, page 12, lines 18-25 of Applicants' specification disclose cell type-specific promoters such as the β-casein promoter, the phosphoenolpyruvate carboxykinase promoter, and the uteroglobin promoter, while page 12, lines 11-17 disclose tissue-specific promoters such as the promoter for tyrosinase, carcinoembryonic antigen, alpha fetoprotein, and myelin basic protein. Applicants' specification also discloses methods for identifying cell type-specific and tissue-specific promoters. For example, page 12, lines 7-10 of Applicants' specification discloses identifying cell type-specific promoters by searching published literature or sequence databases. In addition, the section extending from page 13, line 16 to page 14, line 6 of Applicants' specification discloses using standard methods such as nucleic acid hybridization or immunoassays to identify cell type-specific promoters.

Moreover, Applicants' specification discloses multiple examples of therapeutic gene sequences (see, the section extending from page 23, line 13 to page 25, line 10) and fully describes heat shock elements and HSF-1 (see, the section extending from page 18, line 16 to page 21, line 18). Thus, a person having ordinary skill in the art reading Applicants' specification would have appreciated that Applicants invented the presently claimed invention.

In light of the above, Applicants respectfully request withdrawal of the rejection of claims 9, 15, 35, 37-43, 46-51, 53, 55-61, and 64-67 under 35 U.S.C. § 112, first paragraph.

The Examiner also rejected claims 9, 15, 34-43, and 45-67 under 35 U.S.C. § 112, first paragraph, because:

> the specification, while being enabling for a composition comprising a nucleic acid, wherein said nucleic acid comprises: (a) a cell type-specific promoter of SEQ ID NO:1; (b) a therapeutic gene sequence operably linked to said cell type-specific promoter; (c) an amplification promoter element for amplifying transcription of said therapeutic gene in said therapeutic gene [sic] in said specific cell type; and (d) a sequence encoding a transcription activator for activating said amplification promoter element, wherein said amplification promoter element comprises at least an HSE and said transcriptional activator is HSF-1; does not

> reasonably provide enablement for a composition comprising a nucleic acid, wherein said nucleic acid comprises any cell type-specific promoter, any amplification promoter element and any sequence encoding a transcription activator for activating said amplification promoter element.

The Examiner also stated that:

> Apart from the human Tyr300 (SEQ ID NO:1) promoter which is transcriptionally silent in all of the non-melanoma cells tested, the instant specification fails to teach any other tyrosine promoter element that also has the same promoter activity as that of Tyr300, let alone for any other cell-type specific promoter. It is unclear which other cell-type specific promoters would possess the same promoter activity as that of human Tyr300, particularly it has been known in the art that tissue-specific promoters (e.g., albumin, PSA, MCK, GFAP, NSE) are often either **very weak and/or leaky**. Additionally, the instant specification fails to teach any other amplification promoter element and its corresponding encoded transcription activator to act in conjunction with the Tyr300 promoter to obtain the desired results as those obtained for the HSE-Tyr-300/HSF-1 feedback loop system.

Applicants respectfully disagree. A person having ordinary skill in the art at the time Applicants filed would have been able to make and use the originally claimed invention without undue experimentation. To further prosecution, however, independent claims 9 and 15 have been amended to recite that the amplification promoter element is an HSE and the transcription activator is HSF-1. A person having ordinary skill in the art at the time Applicants filed would have been able to make and use the presently claimed compositions without undue experimentation. In fact, a person having ordinary skill in the art at the time Applicants filed, using common molecular cloning techniques, would have been able to follow the extensive teachings provided throughout Applicants' specification to make a composition containing nucleic acid having a cell type-specific promoter, a therapeutic gene sequence, an HSE, and a sequence encoding HSF-1. This is particularly true given the extensive teachings regarding cell type-specific promoters provided in the section of Applicants' specification extending from page 11, line 13 to page 14, line 6. Moreover, a person having ordinary skill in the art at the time Applicants filed would have been able to assess mRNA levels produced by cells *in vitro* using,

for example, standard RT-PCR assays as described in Example 7 of Applicants' specification. Thus, the present claims are fully enabled.

In light of the above, Applicants respectfully request withdrawal of the rejection of claims 9, 15, 35, 37-43, 46-51, 53, 55-61, and 64-67 under 35 U.S.C. § 112, first paragraph.

CONCLUSION

Applicants submit that claims 9, 15, 35, 37-43, 46-51, 53, 55-61, and 64-67 are in condition for allowance, which action is requested. The Examiner is invited to call the undersigned agent at the telephone number below if such will advance prosecution of this application. The Commissioner is authorized to charge any fees or credit any overpayments to Deposit Account No. 06-1050.

Respectfully submitted,

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